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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,941	12/13/2004	Alexander Berthold Hendrik Bakker	2578-6723us	7383

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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
09/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary	Application No.	Applicant(s)	
	10/517,941	BAKKER ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,6,12,15,17,18 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,6,12,15,17,18 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

1. In the remarks filed on 05/27/2008 in response to the Office Action of 02/07/2008, Applicant canceled claims 1, 2, 5, 7-11, 13-14, 16, 27- 49 and 51 and amended claims 3, 4, 6, 12, 15, 17 and 50. Thus, claims 3, 4, 6, 12, 15, 17-18 and 50 are pending and subject to examination.

Maintained claim rejections

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 6, 12, 15, 17 and 18 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. As iterated in the prior Office action, In the Specification adequate written description is offered for the antibodies denominated in Table 1 (i.e., SC02-008, SC02-009, SC02-010, SC02-011, SC02-012, SC02-021, SC02-022, and SC02-023). These **antibodies** (which is the specific and descriptive way of designating the molecules of the invention instead of the recitation "a human binding molecule") contain both the

variable heavy and light chains and therefore are described fully and but not the full breadth of the claims (drawn to human binding molecules comprising the heavy chain CDR3 (SEQ ID NO 22) meets the written description provision of 35 U.S.C. §112, first paragraph. This is because the art, at the time that the invention was made, does not show that a CDR3 is universally solely responsible for antigen binding. The prior art does not show screening for antibodies by just defining CDR3. The methods rely on using an entire V_H or V_L and screening random complimentary chains. The prior art does not support a definition of an antibody structure solely by defining the CDR3 sequence of a V_H or V_L antigen (Klimka et al., British Journal of Cancer 83: 252-260, 2000; Beiboer et al., J. Mol. Biol. 296:833, 2000; MacCallum et al., J. Mol. Biol. 262: 732-745, 1996).

On page 5 Applicants argue that the human binding molecule comprising the CDR3 sequence of the antibody SC02-021 constitutes adequate description for the genus claimed. The arguments were carefully considered but not found persuasive because the specification does not provide any examples to support that CDR3 is the sole determinant of the binding specificity. The Specification discloses the CDR3 with the SEQ ID NO: 22 in the context of an antibody, which would offer the structural support for the correct orientation of the binder towards the antigen coupled with other domains that actively participate in binding. However, the presence of one CDR has to be complemented by the presence of at least the full complement of CDR from the variable region of which the respective CDR is part of in order for an antibody to be described (see supra). For instance, in the art, it is commonly known that antigen

binding is primarily mediated by the CDRs but more highly conserved framework segments are mainly involved in supporting CDR loop conformations and, in some cases, framework residues also contact the antigen (Vajdos et al., J. Mol. Biol., 320: 415-428, 2002- p.416, left col. last paragraph Therefore the rejection is maintained for the amended claim 3 as an independent claim and for the claims 6, 12, 15, 17 and 18 as being dependent from claim 3.

3. Claims 3, 4, 6, 12, 15, 17-18 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some specific antibodies described in the table I of the specification, does not reasonably provide enablement for genus of human binding molecules only comprising the SEQ ID No: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection has two components which will be treated separately below. The first component relates to obtaining a human binding molecule that is defined by the CDR3 (SEQ ID NO: 22). As presented supra such a molecule lacks adequate written description. In order to be functional, such a molecule has to be an antibody which has necessary requirements (which are attained in the antibodies of Table I of the instant Application). The art at the time that the invention was made describes a screening process using a mouse V_L and a human V_H library with CDR3 and FR4 retained from the mouse V_H. After obtaining antibodies, the V_H was screened against a human V_L

library to obtain antibodies that bound antigen (Klimka et al., British Journal of Cancer 83: 252-260, 2000). Another screening process is described as using the entire mouse heavy chain and a human light chain library. After obtaining antibodies, one V_L was combined with a human V_H library with the CDR3 of the mouse retained. Antibodies capable of binding antigen were obtained (Beiboer et al., J. Mol. Biol. 296:833, 2000). However, the specification does not disclose that the antibody containing a CDR3 of the V_H chain alone can be transferred to just any framework and paired with just any V_L chain and retain antigen binding. The specification does not provide any examples to support that CDR3 of the V_H or V_L is solely responsible for antigen binding and this another essential step missing since it was known in the art that a number of residues outside the CDRs make antigen contacts and residues in the CDRs are important for backbone conformations (MacCallum et al., J. Mol. Biol. 262: 732-745, 1996). Thus, summarizing, the prior art does not show that a CDR3 is universally solely responsible for antigen binding. The prior art does not show screening for antibodies by just defining CDR3. The methods rely on using an entire V_H or V_L and screening random complimentary chains. The prior art does not support a definition of an antibody structure solely by defining the CDR3 sequence of a V_H or V_L.

The working examples disclosed in the specification provide enablement only for the antibodies in table I but not for the other antibodies disclosed. Therefore, it is considered that, because of the large quantity of experimentation necessary to generate the unknown number of potentially agonistic binding molecules recited in the claims and possibly screen the same for activity; the lack of direction/guidance presented in the

specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the state of the prior art which establishes the unpredictability regarding obtaining antibodies with desired properties based on one CDR only; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

With respect to the second component, the ability of the antibodies to have agonistic properties, the desired property is shown for the antibodies designated as SC02-008 and SC02-023 only. Other than this working example (shown in Fig.14 A and B), the specification states that it is to be expected that at least one of the antibodies stimulate T-cell proliferation (and thus having the agonistic properties claimed). A mere prophetic statement does not constitute adequate guidance for the genus of the antibodies sought after.

Therefore, it is considered that, because of the large quantity of experimentation necessary to generate the unknown number of potentially agonistic binding molecules recited in the claims and possibly screen the same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

On page 5 Applicants argue that the amended claims are now enabled because the antibody SC02-021 (which is part of the antibodies presented in Table I) comprises

a defined CDR3 and this would be enough to satisfy the enablement requirement. The arguments were carefully considered but not found persuasive because while the antibody SC02-021 would be considered enabled for binding the human OX-40 receptor, the human binding molecule comprising just the CDR3 is not enabled, as presented supra. Applicants are arguing that a single means, AB SC02-021, is enabling of an entire genus. Moreover, absent an amount of experimentation that is considered undue, the agonistic properties of such an antibody are not determined; the only working examples providing enablement in this respect for the antibodies designated SC02-008 and SC02-023 only.

Conclusion

4. No claims are allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/ Ph.D.

Primary Examiner, Art Unit 1647